```
NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
NEWS  2          "Ask CAS" for self-help around the clock
NEWS  3  JAN 27  Source of Registration (SR) information in REGISTRY updated
                 and searchable
NEWS  4  JAN 27  A new search aid, the Company Name Thesaurus, available in
                 CA/CAplus
NEWS  5  FEB 05  German (DE) application and patent publication number format
                 changes
NEWS  6  MAR 03  MEDLINE and LMEDLINE reloaded
NEWS  7  MAR 03  MEDLINE file segment of TOXCENTER reloaded
NEWS  8  MAR 03  FRANCEPAT now available on STN
NEWS  9  MAR 29  Pharmaceutical Substances (PS) now available on STN
NEWS 10  MAR 29  WPIFV now available on STN
NEWS 11  MAR 29  No connect hour charges in WPIFV until May 1, 2004
NEWS 12  MAR 29  New monthly current-awareness alert (SDI) frequency in RAPRA
NEWS 13  APR 26  PROMT: New display field available
NEWS 14  APR 26  FIPAT/IFIUDB/IFICDB: New super search and display field
                 available
NEWS 15  APR 26  LITALERT now available on STN
NEWS 16  APR 27  NLDB: New search and display fields available

NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
              MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 13 APRIL 2004
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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FILE 'HOME' ENTERED AT 08:32:07 ON 28 APR 2004

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    0.21       0.21

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STRUCTURE FILE UPDATES:   26 APR 2004  HIGHEST RN 676992-14-6
DICTIONARY FILE UPDATES:  26 APR 2004  HIGHEST RN 676992-14-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

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Crossover limits have been increased.  See HELP CROSSOVER for details.
```

Experimental and calculated property data are now available. For more
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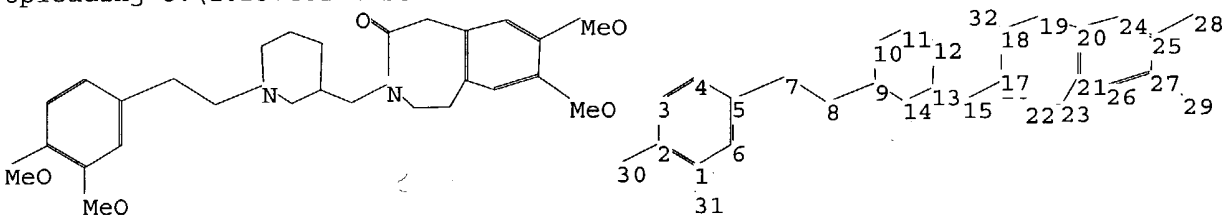
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading c:\10257481-1.str



chain nodes :
7 8 15 16 17 18 19 22 23 28 29 30 31 32
ring nodes :
1 2 3 4 5 6 9 10 11 12 13 14 20 21 24 25 26 27
chain bonds :
1-31 2-30 5-7 7-8 8-9 13-15 15-16 16-22 17-18 18-19 18-32 19-20 21-23
22-23 25-28 27-29
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 9-10 9-14 10-11 11-12 12-13 13-14 20-21 20-24
21-26 24-25 25-27 26-27
exact/norm bonds :
8-9 9-10 9-14 10-11 11-12 12-13 13-14 15-16 16-22 18-32
exact bonds :
1-31 2-30 5-7 7-8 13-15 17-18 18-19 19-20 21-23 22-23 25-28 27-29
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 20-21 20-24 21-26 24-25 25-27 26-27

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:Atom 21:Atom 22:CLASS 23:CLASS 24:Atom 25:Atom 26:Atom 27:Atom
28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Structure attributes must be viewed using STN Express query preparation.

=> s l1
SAMPLE SEARCH INITIATED 08:33:07 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 1 TO ITERATE

100.0% PROCESSED 1 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

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FULL FILE PROJECTIONS:  ONLINE   **COMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:             1 TO        80
PROJECTED ANSWERS:                0 TO         0

L2             0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 08:33:24 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      3 TO ITERATE

100.0% PROCESSED       3 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

L3             0 SEA SSS FUL L1

=> file polymers
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   155.84     156.05

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FILE 'USPAT2' ENTERED AT 08:33:38 ON 28 APR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

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=> s cilobradine
L4          18 CILOBRADINE

=> s l4 and hypertrop?
L5          13 L4 AND HYPERTROP?

=> dis l5 1-13 bib abs

L5   ANSWER 1 OF 13  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2001:780659  CAPLUS
DN   135:335152
TI   Use of bradycardiac substances in the treatment of myocardial diseases
     associated with hypertrophy and novel drug combinations
IN   Daemmgen, Juergen; Guth, Brian; Seidler, Randolph
PA   Boehringer Ingelheim Pharma K.-G., Germany
SO   PCT Int. Appl., 13 pp.
     CODEN: PIXXD2
DT   Patent
LA   German
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2001078699     A2    20011025       WO 2001-EP4034   20010407
     WO 2001078699     A3    20020620
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
             HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
             RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
             VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     DE 10018401       A1    20011025       DE 2000-10018401 20000413
     EP 1276476        A2    20030122       EP 2001-949281   20010407
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

	BR 2001009996	A	20030527	BR 2001-9996	20010407
	JP 2003535050	T2	20031125	JP 2001-576000	20010407
	BG 107103	A	20030430	BG 2002-107103	20020913
	NO 2002004924	A	20021011	NO 2002-4924	20021011
	US 2004014795	A1	20040122	US 2003-257481	20030613
PRAI	DE 2000-10018401	A	20000413		
	WO 2001-EP4034	W	20010407		

AB The invention relates to a novel use of bradycardiac substances such as a Ca++ channel blocker, beta-receptor blockers or if channel blockers, the if channel blockers being preferred. The substances are optionally used in combination with a cardio-active substance for inducing the regression of myocardial diseases associated with **hypertrophy**, in particular for treating idiopathic **hypertrophic** cardiomyopathies (HCM) in humans and domestic animals. Thus 1.25 mg **cilobradine** was encapsulated in capsules that were prepared from 82.75 mg lactose monohydrate and 55.3 mg corn starch.

L5 ANSWER 2 OF 13 IFIPAT COPYRIGHT 2004 IFI on STN
AN 10507592 IFIPAT;IFIUDB;IFICDB
TI USE OF BRADYCARDIAC SUBSTANCES IN THE TREATMENT OF MYOCARDIAL DISEASES ASSOCIATED WITH **HYPERTROPHY** AND NOVEL MEDICAMENT COMBINATIONS
INF Daemmgen; Juergen, Ochsenhausen, DE
Guth; Brian, Warthausen, DE
Seidler; Randolph, Biberach, DE
IN Daemmgen Juergen (DE); Guth Brian (DE); Seidler Randolph (DE)
PAF Unassigned
PA Unassigned Or Assigned To Individual (68000)
AG BOEHRINGER INGELHEIM CORPORATION, 900 RIDGEBURY ROAD, P. O. BOX 368, RIDGEFIELD, CT, 06877, US

PI	US 2004014795	A1	20040122	
AI	US 2003-257481		20030613	
	WO 2001-EP4034		20010407	
			20030613	PCT 371 date
			20030613	PCT 102(e) date
PRAI	DE 2000-100184014		20000413	
FI	US 2004014795		20040122	

DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
CLMN 8
AB The present invention relates to the new use of bradycardiac substances such as a Ca++ channel blocker, beta-receptor blocker or if channel blocker, the if channel blockers being preferred, optionally in combination with a cardioactive substance for inducing the regression of myocardial diseases accompanied by **hypertrophy**, particularly for the treatment of idiopathic **hypertrophic** cardiomyopathies (HCM) in humans and domestic pets.
CLMN 8

L5 ANSWER 3 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AN 2003:45936 SCISEARCH
GA The Genuine Article (R) Number: 630VW
TI Comparison between invasive hemodynamic measurements and noninvasive assessment of left ventricular diastolic function by use of Doppler echocardiography in healthy anesthetized cats
AU Schober K E (Reprint); Fuentes V L; Bonagura J D
CS Univ Missouri, Coll Vet Med, Dept Vet Med & Surg, Columbia, MO 65211 USA (Reprint); Univ Leipzig, Fac Med Vet, Dept Small Anim Med, D-04103 Leipzig, Germany
CYA USA; Germany
SO AMERICAN JOURNAL OF VETERINARY RESEARCH, (JAN 2003) Vol. 64, No. 1, pp. 93-103.
Publisher: AMER VETERINARY MEDICAL ASSOC, 1931 N MEACHAM RD SUITE 100, SCHAUMBURG, IL 60173-4360 USA.

ISSN: 0002-9645.
DT Article; Journal
LA English
REC Reference Count: 73
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Objective-To compare Doppler echocardiographic variables of left ventricular 0) function with those obtained invasively via cardiac catheterization under a range of hemodynamic conditions.

Animals-7 healthy anesthetized cats U to 3 years of age).

Procedure-Cats were anesthetized and instrumented to measure the time constant of isovolumic relaxation (tau [tau]), LV end-diastolic pressure (LVEDP), peak negative and positive rate of change of LV pressure, arterial blood pressure, and cardiac output. Echocardiographic variables of diastolic function (isovolumic relaxation time [IVRT], early LV flow propagation velocity [Vp], transmitral and pulmonary venous flow velocity indices, and LV tissue Doppler imaging indices) were measured simultaneously over a range of hemodynamic states induced by treatments with esmolol, dobutamine, **cilobradine**, and volume loading. Correlation between invasive and noninvasive measures of LV filling was determined by univariate and multivariate regression analyses.

Results-Significant correlations were found between tau and IVRT, peak Vp, peak late transmitral flow velocity, and peak systolic pulmonary venous flow velocity. A significant correlation was found between LVEDP and early diastolic transmitral flow velocity (peak E) and the ratio of peak E to peak Vp, but not between LVEDP and peak Vp.

Conclusions and Clinical Relevance-IVRT and Vp can be used as noninvasive indices of LV relaxation; Vp was independent of preload and heart rate in this study. The E:Vp ratio may be useful as an indicator of LV filling pressure.

L5 ANSWER 4 OF 13 USPATFULL on STN
AN 2004:19491 USPATFULL
TI Use of bradycardiac substances in the treatment of myocardial diseases associated with **hypertrophy** and novel medicament combinations
IN Daemmgen, Juergen, Ochsenhausen, GERMANY, FEDERAL REPUBLIC OF
Guth, Brian, Warthausen, GERMANY, FEDERAL REPUBLIC OF
Seidler, Randolph, Biberach, GERMANY, FEDERAL REPUBLIC OF
PI US 2004014795 A1 20040122
AI US 2003-257481 A1 20030613 (10)
WO 2001-EP4034 20010407
PRAI DE 2000-10018401 20000413
DT Utility
FS APPLICATION
LREP BOEHRINGER INGELHEIM CORPORATION, 900 RIDGEBURY ROAD, P. O. BOX 368, RIDGEFIELD, CT, 06877
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 238
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the new use of bradycardiac substances such as a Ca.sup.++ channel blocker, beta-receptor blocker or i.sub.f channel blocker, the i.sub.f channel blockers being preferred, optionally in combination with a cardioactive substance for inducing the regression of myocardial diseases accompanied by **hypertrophy**, particularly for the treatment of idiopathic **hypertrophic** cardiomyopathies (HCM) in humans and domestic pets.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 13 USPATFULL on STN
AN 2003:85867 USPATFULL
TI Oral delivery formulation
IN Compton, Bruce Jon, Lexington, MA, UNITED STATES
Solari, Nancy E., West Newton, MA, UNITED STATES

Flangan, Margaret A., Stow, MA, UNITED STATES
PI US 2003059471 A1 20030327
AI US 2001-997277 A1 20011129 (9)
RLI Continuation of Ser. No. US 1998-55560, filed on 6 Apr 1998, ABANDONED
PRAI US 1997-69501P 19971215 (60)
US 1998-73867P 19980204 (60)
DT Utility
FS APPLICATION
LREP Stephen J Gaudet, 68H Stiles Road, Salem, NH, 03079
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2950
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Flakes containing drugs and methods for forming and using such flakes are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 6 OF 13 USPATFULL on STN
AN 2002:17328 USPATFULL
TI Dha-pharmaceutical agent conjugates of taxanes
IN Shashoua, Victor, Brookline, MA, UNITED STATES
Swindell, Charles, Merion, PA, UNITED STATES
Webb, Nigel, Bryn Mawr, PA, UNITED STATES
Bradley, Matthews, Layton, PA, UNITED STATES
PI US 2002010208 A1 20020124
US 6602902 B2 20030805
AI US 2001-846838 A1 20010501 (9)
RLI Continuation of Ser. No. US 1998-135291, filed on 17 Aug 1998, ABANDONED
Continuation of Ser. No. US 1996-651312, filed on 22 May 1996, GRANTED, Pat. No. US 5795909
DT Utility
FS APPLICATION
LREP Edward R. Gates, Esq., Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN 14 Drawing Page(s)
LN.CNT 2437
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides conjugates of cis-docosahexaenoic acid and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 7 OF 13 USPATFULL on STN
AN 2001:90260 USPATFULL
TI Fatty acid-pharmaceutical agent conjugates
IN Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
Swindell, Charles S., Merion, PA, United States
Shashoua, Victor E., Brookline, MA, United States
PI US 2001002404 A1 20010531
US 6576636 B2 20030610
AI US 2000-730450 A1 20001205 (9)
RLI Continuation of Ser. No. US 1996-651428, filed on 22 May 1996, ABANDONED
DT Utility
FS APPLICATION
LREP Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
CLMN Number of Claims: 12
ECL Exemplary Claim: 1

DRWN 14 Drawing Page(s)
LN.CNT 2511
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides conjugates of fatty acids and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 8 OF 13 USPATFULL on STN
AN 1998:98932 USPATFULL
TI DHA-pharmaceutical agent conjugates of taxanes
IN Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles S., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
PA Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)
PI US 5795909 19980818
AI US 1996-651312 19960522 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Wolf, Greenfield & Sacks, P.C.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 27 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 2451
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 9 OF 13 USPAT2 on STN
AN 2002:17328 USPAT2
TI Dha-pharmaceutical agent conjugates to improve tissue selectivity
IN Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles E., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Layton, PA, United States
PA Protarga, Inc., King of Prussia, PA, United States (U.S. corporation)
PI US 6602902 B2 20030805
AI US 2001-846838 20010501 (9)
RLI Continuation of Ser. No. US 1998-135291, filed on 17 Aug 1998, now abandoned Continuation of Ser. No. US 1996-651312, filed on 22 May 1996, now patented, Pat. No. US 5795909
DT Utility
FS GRANTED
EXNAM Primary Examiner: Krass, Frederick; Assistant Examiner: Jagoe, Donna
LREP Wolf, Greenfield, & Sacks, P.C.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 27 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 2583
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides conjugates of cis-docosahexaenoic acid and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 10 OF 13 USPAT2 on STN

AN 2001:90260 USPAT2
TI Method of treating a liver disorder with fatty acid-antiviral agent conjugates
IN Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
Swindell, Charles S., Merion, PA, United States
Shashoua, Victor E., Brookline, MA, United States
PA Protarga, Inc., King of Prussia, PA, United States (U.S. corporation)
PI US 6576636 B2 20030610
AI US 2000-730450 20001205 (9)
RLI Continuation of Ser. No. US 1996-651428, filed on 22 May 1996, now abandoned
DT Utility
FS GRANTED
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Wolf, Greenfield & Sacks, P.C.
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 27 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 2654
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides conjugates of fatty acids and antiviral agents useful in treating liver disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 11 OF 13 WPINDEX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-204046 [20] WPINDEX
DNC C2004-080618
TI Use of cyclic amine derivative in the preparation of composition for treating or preventing heart failure due to e.g. myocardial infarction.
DC B02 B07
IN DAEMMGEN, J; GUTH, B; SEIDLER, R
PA (BOEH) BOEHRINGER INGELHEIM PHARMA GMBH & CO KG
CYC 1
PI CA 2435526 A1 20040125 (200420)* EN 73
ADT CA 2435526 A1 CA 2003-2435526 20030718
PRAI EP 2002-16600 20020725
AN 2004-204046 [20] WPINDEX
AB CA 2435526 A UPAB: 20040324
NOVELTY - In the preparation of a composition for the treatment or prevention of heart failure, a cyclic amine derivative (I/I'), its enantiomer, diastereomer, N-oxide or salt is used.
DETAILED DESCRIPTION - In the preparation of a composition for the treatment or prevention of heart failure, a cyclic amine derivative of formula (I) or (I'), its enantiomer, diastereomer, N-oxide or salt is used.
R1 = R2, CF3, nitro, amino, 1-3C alkylamino or 1-3C dialkylamino;
R2 = H, halo, OH, 1-3C alkoxy, 1-3C phenylalkoxy or 1-3C alkyl;
R1+R2 = 1-2C alkylenedioxy;
E = 1-3C straight-chain alkylene (optionally substituted by 1-3C alkyl);
A = -CH2-CH2-, -CH=CH-, -CH2-CO-, -NH-CO-, -CO-CO- or -CHOH-CO-;
B = -CH2-CH2, -CH2CO- or -CH2CS-;
G = 1-4C straight-chain alkylene (optionally substituted by 1-3C alkyl) or -G1-G2-
G1 = 2-4C straight chain alkylene (optionally substituted by 1-3C alkyl) attached to N;
G2 = oxa, thia, (methyl)imino, sulfinyl or sulfonyl (all attached to R);
R = phenyl (substituted by R3, R4 and R5);
R3 = H, halo, 1-3C alkyl, 1-3C alkoxy, OH, nitro, CN, or CF3;
R4 = H, alkoxy, 1-3C alkylsulfonyloxy, amino, 1-3C (di)alkylamino, or 2-3C alkanoylamino;
R3+R4 = 1-2C alkylenedioxy;

R5 = H, halo, OH, 1-3C alkyl, or 1-3C alkoxy;
m = 1 - 5;
n = 0 - 2;
m+n = 3 - 5;
A' = -CH2-, -CH2-CH2-, or -CH=CH-;
B' = -CH2-, -CH2-CH2-, -CO- or -CH2CO-;
G' = 1-6C straight chain alkylene (optionally substituted by 1-3C alkyl) or -G'1-G'2-;
G'1 = 2-5C straight-chain alkylene (optionally substituted by 1-3C alkyl) attached to N;
G'2 = oxa, thia, sulfinyl, sulfonyl, or imino (optionally substituted by 1-3C alkyl) attached to R';
m' = 1 - 6;
n' = 0 - 3;
m'+n' = 3 - 6;
R' = 5- membered heteroaryl containing O, S and/or 1-2N, or 6-membered heteroaryl containing 1 - 2 N (both optionally mono- or di-substituted by halo, alkyl, OH, (phenyl)alkoxy, Ph, dimethoxyphenyl, nitro, amino, acetylamino, carbamoylamino, N-alkylcarbamoylamino, hydroxymethyl, (alkyl)mercapto, alkylsulfinyl, alkylsulfonyl, alkylsulfonyloxy, alkylsulfonylamino, alkoxycarbonylmethoxy, carboxymethoxy, methylenedioxy, or ethylenedioxy (where imino group in the ring is substituted by alkyl, phenylalkyl or Ph)), indolyl (optionally substituted by benzyl, benzyloxy, benzylamino (all optionally mono- to tri-substituted by methoxy or methyl), (di)methylamino, methoxy, acetoxy, CF3, trichloromethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, CN, cyclohexyl, trimethoxyphenyl, trihalophenyl, dihaloaminophenyl) or naphthyl (optionally substituted by 1-2C alkylenedioxy, or mono- or disubstituted by halo, alkyl, OH, alkoxy, alkylsulfonyloxy, nitro, amino or alkanoylamino), benzyloxy, 4,5,6,7-tetrahydrobenzo(b)thienyl or phenyl (optionally substituted by 1-2C alkylenedioxy, halo, alkyl, OH, alkoxy, phenylalkoxy, nitro, amino, alkanoylamino, alkylsulfonylamino, bis(alkylsulfonyl)amino, alkylsulfonyloxy, CF3, trifluoromethoxy, trifluoromethylsulfonyloxy, or disubstituted by halo, alkyl, or alkoxy, trialkoxyphenyl, tetraalkylphenyl or dihaloaminophenyl.
Provided that:
(a) when A is -CH2-CH2-, -CH=CH-, -CH2CO- or -NH-CO- then B is -CH2-CH2-, -CH2CO- or CH2CS-; or when A = -CO-CO- or -CHOH-CO- then B is -CH2-CH2-;
(b) when B' is -CH2- or -CO-, then R' is also chosen from phenyl (optionally substituted by 1-2C alkylenedioxy, halo, alkyl, OH, alkoxy, phenylalkoxy, nitro, amino, alkanoylamino, alkylsulfonylamino, bis(alkylsulfonyl)amino, alkylsulfonyloxy, CF3, trifluoromethoxy, trifluoromethylsulfonyloxy or disubstituted by halo, alkyl, or alkoxy, trialkoxyphenyl, tetraalkylphenyl or dihaloaminophenyl.
ACTIVITY - Cardiant; Cardiovascular-Gen; Hypotensive; Respiratory-Gen; Thrombolytic; Antiarrhythmic.
An experiment was carried out to compare visual side effect of the test compound (Cilobradine) and a control (Zatebradine). The reduction of heart rate was measured after the administration of chosen doses. A reduction of 75 % of the heart rate is obtained with test while a reduction of 44 % of the heart rate is obtained with control.
MECHANISM OF ACTION - Hyperpolarization activated cation current channel (HCN) blocker.
USE - For the treatment or prevention of heart failure (claimed) of aetiology diagnosed as a consequence or complication of any other condition , disease or disorder e.g. cardiac insufficiency, cardiac failure, heart insufficiency, myocardial failure, myocardial insufficiency, heart muscle insufficiency, cardiac muscle insufficiency, insufficient cardiac output, heart muscle weakness, cardiac collapse, cardiac syncope, chronic heart failure, acute heart failure, heart decompensation, cardial decompensation, diastolic heart failure, right sided heart failure, systolic heart failure, left ventricular heart failure, left sided heart failure, biventricular heart failure, congestive heart failure, systolic dysfunction, diastolic dysfunction, ischemic heart

diseases, including myocardial infarction, right ventricular infarction, chronic ischemia, coronary heart diseases, hypertension, primary pulmonary hypertension, secondary pulmonary hypertension, pulmonary embolism, pulmonary arterial stenosis, chronic obstructive pulmonary disease, restrictive cardiomyopathies, dialated cardiomyopathies due to infectious, toxic, metabolic, familial or unknown reasons, myocarditis, congenital anomalies, tachycardias and ventricular hypertrophy secondary to genetic or volvular disorders such as tricuspid valve insufficiency, mitral and/or aortic valve disorders, heart infarcts, thyroid diseases and anemia.

ADVANTAGE - The compound exhibits pharmacologically longer duration of action, dose for dose potency and cardioselectivity, resulting in decreased or absent side effects.

Dwg.0/3

L5 ANSWER 12 OF 13 WPINDEX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-111133 [12] WPINDEX
DNC C2004-045298
TI Use of **cilobradine** or its salt for the treatment or prevention of heart failure such as cardiac insufficiency, cardiac failure.
DC B02
IN DAEMMGEN J DBH & CO, KG; GUTH B DBH & CO, KG; SEIDLER R UBH & CO, KG; DAEMMGEN, J; GUTH, B; SEIDLER, R
PA (BOEH) BOEHRINGER INGELHEIM PHARMA GMBH & CO KG
CYC 106
PI EP 1362590 A1 20031119 (200412)* EN 15
R: AL AT BE CH CY CZ DE DK EE ES FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
EP 1362590 B1 20040107 (200412) EN
R: AL AT BE CH CY CZ DE DK EE ES FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
WO 2004011006 A1 20040205 (200413) EN
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
EP 1362590 A8 20040225 (200416) EN
R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI SK TR
DE 60200160 E 20040212 (200419)
ADT EP 1362590 A1 EP 2002-16602 20020725; EP 1362590 B1 EP 2002-16602 20020725; WO 2004011006 A1 WO 2003-EP7929 20030721; EP 1362590 A8 EP 2002-16602 20020725; DE 60200160 E DE 2002-00200160 20020725, EP 2002-16602 20020725
FDT DE 60200160 E Based on EP 1362590
PRAI EP 2002-16602 20020725
AN 2004-111133 [12] WPINDEX
AB EP 1362590 A UPAB: 20040218

NOVELTY - In the preparation of a pharmaceutical composition for the treatment or prevention of heart failure, a **cilobradine** (A1) or its salt is used.

ACTIVITY - Cardiant; Vasotropic; Cardiovascular-Gen.; Hypotensive; Thrombolytic; Respiratory-Gen.; Antithyroid; Antianemic.

MECHANISM OF ACTION - None given.

USE - In the preparation of a pharmaceutical composition for the treatment or prevention of heart failure (claimed) such as cardiac insufficiency, cardiac failure, heart insufficiency, myocardial failure, myocardial insufficiency, heart muscle insufficiency, cardiac muscle insufficiency, insufficient cardiac output, heart muscle weakness, cardiac muscle weakness, cardiac collapse, cardiac syncope, chronic heart failure, acute heart failure, heart decompensation, cardiac decompensation, cardial decompensation, diastolic heart failure, right sided heart failure,

systolic heart failure, left ventricular heart failure, left sided heart failure, biventricular heart failure and congestive heart failure; for the treatment of heart failure of any aetiology means heart failure diagnosed as a consequence or complication of any other condition, disease or disorder such as systolic dysfunction, diastolic dysfunction, ischemic heart diseases, including myocardial infarction, right ventricular infarction and chronic ischemia, coronary heart diseases, hypertension, primary pulmonary hypertension, secondary pulmonary hypertension, pulmonary embolism, pulmonary arterial stenosis, chronic obstructive pulmonary disease, restrictive cardiomyopathies, dilated cardiomyopathies due to infectious, toxic, metabolic, familial or unknown reasons, myocarditis, congenital anomalies, tachycardias and ventricular **hypertrophy** secondary to genetic or valvular disorders such as tricuspid valve insufficiency, mitral and aortic valve disorders, heart infarcts, thyroid diseases and anemia.

ADVANTAGE - (A1) provides an advantage over zatebradine not only in terms of its pharmacologically longer duration of action and dose for dose potency, but more importantly in its cardioselectivity resulting in decreased or absent visual side effects when compared to therapeutic doses of zatebradine. (A1) has intrinsically different pharmacological properties than zatebradine, which permit full cardiac ion channel blockade with absent or diminished retinal effects. (A1) able to reduces the mortality and morbidity associated with heart failure of any aetiology.

Dwg.0/3

L5 ANSWER 13 OF 13 WPINDEX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-011919 [02] WPINDEX
DNC C2002-003158
TI Medicament for treating **hypertrophy**-related myocardial disease, containing bradycardic agent, preferably **cilobradine**, and optionally another cardiac drug.
DC B02
IN DAEMMGEN, J; GUTH, B; SEIDLER, R; DAMMGEN, J
PA (BOEH) BOEHRINGER INGELHEIM PHARMA KG; (BOEH) BOEHRINGER INGELHEIM PHARMA GMBH & CO KG; (DAEM-I) DAEMMGEN J; (GUTH-I) GUTH B; (SEID-I) SEIDLER R
CYC 96
PI DE 10018401 A1 20011025 (200202)* 5
WO 2001078699 A2 20011025 (200202) GE
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001070484 A 20011030 (200219)
NO 2002004924 A 20021011 (200304)
EP 1276476 A2 20030122 (200308) GE
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
SK 2002001458 A3 20030304 (200321)
KR 2002089453 A 20021129 (200322)
CZ 2002003752 A3 20030312 (200324)
BR 2001009996 A 20030527 (200344)
CN 1422153 A 20030604 (200356)
HU 2003000917 A2 20030828 (200363)
JP 2003535050 W 20031125 (200380) 18
US 2004014795 A1 20040122 (200407)
ZA 2002008162 A 20031231 (200408) 28
MX 2002009935 A1 20030201 (200413)
ADT DE 10018401 A1 DE 2000-10018401 20000413; WO 2001078699 A2 WO 2001-EP4034 20010407; AU 2001070484 A AU 2001-70484 20010407; NO 2002004924 A WO 2001-EP4034 20010407, NO 2002-4924 20021011; EP 1276476 A2 EP 2001-949281 20010407, WO 2001-EP4034 20010407; SK 2002001458 A3 WO 2001-EP4034 20010407, SK 2002-1458 20010407; KR 2002089453 A KR 2002-713688 20021011;

CZ 2002003752 A3 WO 2001-EP4034 20010407, CZ 2002-3752 20010407; BR 2001009996 A BR 2001-9996 20010407, WO 2001-EP4034 20010407; CN 1422153 A CN 2001-807959 20010407; HU 2003000917 A2 WO 2001-EP4034 20010407, HU 2003-917 20010407; JP 2003535050 W JP 2001-576000 20010407, WO 2001-EP4034 20010407; US 2004014795 A1 WO 2001-EP4034 20010407, US 2003-257481 20030613; ZA 2002008162 A ZA 2002-8162 20021010; MX 2002009935 A1 WO 2001-EP4034 20010407, MX 2002-9935 20021008

FDT AU 2001070484 A Based on WO 2001078699; EP 1276476 A2 Based on WO 2001078699; SK 2002001458 A3 Based on WO 2001078699; CZ 2002003752 A3 Based on WO 2001078699; BR 2001009996 A Based on WO 2001078699; HU 2003000917 A2 Based on WO 2001078699; JP 2003535050 W Based on WO 2001078699; MX 2002009935 A1 Based on WO 2001078699

PRAI DE 2000-10018401 20000413

AN 2002-011919 [02] WPINDEX

AB DE 10018401 A UPAB: 20020109

NOVELTY - A medicament (A) for treating myocardial diseases associated with **hypertrophy** contains a bradycardic agent (I) and optionally another cardiac drug (II).

ACTIVITY - Cardiant.

In tests in a cat having severe **hypertrophic** cardiomyopathy, oral administration of **cilobradine** (Ia) twice daily at 0.3 mg/kg marked reduced the clinical symptoms (e.g. by reducing pain and normalizing the ECG) and also caused regression of the myocardial **hypertrophy** after 1 and 2 years.

MECHANISM OF ACTION - Calcium ion channel blocker; beta -receptor blocker; if channel blocker.

USE - (A) is used for treating myocardial diseases associated with **hypertrophy** (claimed), especially idiopathic **hypertrophic** cardiomyopathy such as **hypertrophy** of the remaining myocardium after cardiac infarction, ischemic cardiomyopathy, valve-associated **hypertrophy** of the myocardium or myocarditis due to toxic or iatrogenic effects.

ADVANTAGE - As well as alleviating the clinical symptoms, (A) causes regression of the above severe heart conditions. if Channel blockers (I) inhibit rebound increase in cardiac frequency, and have a synergistic effect in combination with (II).

Dwg.0/0

=> s alinidine
L6 442 ALINIDINE

=> s l6 and hypertrop?
L7 11 L6 AND HYPERTROP?

=> dis l6 1-11 bib abs

L6 ANSWER 1 OF 442 BABS COPYRIGHT 2004 BEILSTEIN MDL on STN

AN 6381491 BABS

TI Antiischemic and Antiarrhythmic Activities of Some Novel **Alinidine** Analogs in the Rat Heart

AU Challinor-Rogers, Joanne L.; Rosenfeldt, Franklin L.; Du, Xiao-Jun; McPherson, Grant A.

SO J.Cardiovas.Pharmacol. (1997), 29, 499 - 507
CODEN: JCPCDT

DT Journal

LA English

SL English

AN 6381491 BABS

AB The antiischemic and antiarrhythmic effects of **alinidine** and a number of novel **alinidine** analogs were examined by using perfused rat-heart models. In the isolated working rat heart, the **alinidine** analog TH91:21 (10 $mM); a butyl derivative) significantly increased the postischemic recovery of the heart in terms of both power and efficiency when compared with the control group. In the in

situ perfused heart model, this same compound, along with TH91:22 (10 $mM; a pentyl derivative) also significantly reduced the severity of both ischemia- and reperfusion-induced arrhythmias in both paced and unpaced hearts. Thus this study is the first to demonstrate the potent antiarrhythmic efficacy of two novel **alinidine** analogs TH91:21 and TH91:22, with TH91:21 also demonstrated to be a potent antiischemic agent in the isolated working rat heart. Although the mode of action of these compounds remains unclear, results from this study suggest that it is not simply a result of bradycardia or blockade of K&ATP% channels, two actions these compounds possess. These compounds thus possess a novel and beneficial pharmacologic profile worthy of further study.

L6 ANSWER 2 OF 442 BABS COPYRIGHT 2004 BEILSTEIN MDL on STN
AN 6356071 BABS
TI Heterogeneous characteristics of imidazoline-induced insulin secretion
AU Rustenbeck, Ingo; Leupolt, Lars; Kowalewski, Roland; Hasselblatt, Arnold
SO Naunyn-Schmiedeberg's Arch.Pharmacol. (1999), 359(3), 235 - 242
CODEN: NSAPCC
DT Journal
LA English
SL English
AN 6356071 BABS
AB Imidazolines are regarded as a pharmacological group of insulin secretagogues with one uniform mechanism of action, namely closure of ATP-dependent K%+& channels (K&ATP% channels) and, in consequence, depolarization of the plasma membrane, Ca%2+& influx and stimulation of secretion. This assumption was investigated by measuring insulin secretion from perifused pancreatic islets in response to three imidazoline compounds and comparing the characteristics of secretion with changes in membrane potential and cytostolic Ca%2+& concentration [Ca%2+&]&i% of single $b-cells. Phentolamine (32 $mM) stimulated insulin secretion from perifused mouse islets in the presence of stimulatory (10 mM and 30 mM) and substimulatory (5 mM) glucose concentrations and even in the absence of glucose. Idazoxan in concentrations up to 500 $mM was virtually ineffective in the presence of 5 mM glucose. At 10 mM glucose, there was a moderate but significant increase of secretion by idazoxan, 20 $mM being nearly as effective as 100 $mM. The effect of phentolamine was of slow onset and irreversible in the time frame of the experiments, while the effect of idazoxan was of fast onset and reversible. **Alinidine** also stimulated secretion in the presence of 10 mM glucose with fast and reversible kinetics, but in contrast to idazoxan, 100 $mM was clearly more effective than 20 $mM. These heterogeneous characteristics of secretion were reflected by changes of [Ca%2+&]&i%: the increase of [Ca%2+&]&i% by phentolamine was slow and only partially reversible, whereas idazoxan led to a smaller, but faster and reversible response. The increase of [Ca%2+&]&i% by phentolamine and idazoxan was abolished by the Ca%2+& channel blocker D 600. Suprisingly, all three compounds depolarized the $b-cell plasma membrane from a resting potential of -71 mV to about -36 mV. Again, the effect of phentolamine was slow and that of idazoxan and **alinidine** fast. Thus, the characteristics of phentolamine-induced secretion appear to be attributable to the consequences of K&ATP% channel closure. It is unclear, however, why all three test compounds achieved the same degree of depolarization in spite of their known different efficiency to close K&ATP% channels. Apparently, there are additional mechanisms involved in the action of idazoxan and **alinidine**, which may contribute to the obvious differences in the characteristics of secretion.

L6 ANSWER 3 OF 442 BABS COPYRIGHT 2004 BEILSTEIN MDL on STN
AN 6303149 BABS
TI Cardiac electrophysiological effects of falipamil in the conscious dog: comparison with **alinidine**
AU Boucher, Michel; Chassaing, Claude; Chapuy,Eric
SO Eur.J.Pharmacol. (1996), 306(1-3), 93 - 98
CODEN: EJPHAZ
DT Journal

LA English
SL English
AN 6303149 BABS
AB We studied the cardiac electrophysiological effects of falipamil, a specific bradycardic agent, in conscious dogs, in comparison with those of **alinidine.** Sinus rate, corrected sinus recovery time, and Wenckebach point were measured in six intact dogs. Atrial rate, ventricular rate, and atrial effective refractory period were measured in six atrioventricular-blocked dogs. In both groups, blood pressure was also monitored. Each dog received, with at least a three-day interval, falimapil (hydrochloride) and **alinidine** (hydrobromide) in four successive intravenous injections, 30 min apart, at 0.5, 0.5, 1, and 2 mg kg%-1&. Falipamil increased sinus rate and atrial rate, but decreased ventricular rate, whereas **alinidine** decreased sinus rate and ventricular rate, but increased atrial rate. Falipamil shortened corrected sinus recovery time and increased Wenckebach point, whereas **alinidine** lengthened corrected sinus recovery time and decreased Wenckebach point. Falipamil and **alinidine** increased atrial effective refractory period. Neither falipamil nor **alinidine** modified mean blood pressure in either group. Overall, these results show that (a) falipamil exhibits effects on the electrical activity of the heart, reflecting the predominant direct vagolytic effect of this drug, (b) **alinidine** exhibits effects reflecting the marked antiarrhythmic potential of this agent, and (c) thus indicate that two drugs with almost identical specific bradycardic properties can produce quite different electrophysiological effects in the conscious dog.

L6 ANSWER 4 OF 442 BABS COPYRIGHT 2004 BEILSTEIN MDL on STN
AN 6302834 BABS
TI The novel cardioprotective agent BMS-180448 activates a potassium conductance in cardiac and vascular smooth muscle
AU Lodge, Nicholas J.; Smith, Mark A.
SO Naunyn-Schmiedeberg's Arch.Pharmacol. (1996), 354(4), 444 - 451
CODEN: NSAPCC
DT Journal
LA English
SL English
AN 6302834 BABS
AB The goal of the present study was to further characterize the effects of the novel cardioprotective agent BMS-180448 on potassium fluxes in cardiac and vascular smooth muscle. Exposure of voltage-clamped guinea pig ventricular myocytes to BMS-180448 (300 $mM) produced an inhibition of I&k% followed by the delayed (5.5 +/- 0.5 min) activation of a large time-independent potassium current. At 100 $mM, BMS-180448 produced only inhibition of I&K%. The BMS-180448 activated current was refractory to block by 30 $mM glyburide but was largely inhibited by 100 $mM **alinidine** (84 +/- 6 percent inhibition at +40 mV). Cromakalim (100 $mM)-activated currents were fully inhibited by 3 $mM glyburide and 79 +/- 4 percent blocked by 100 $mM **alinidine.** The current responses to BMS-180448 were unaffected by the inclusion of 10mM UDP (200 $mM ATP) in the pipette. BMS-180448 also produced a concentration-dependent increase in %86&Rb efflux from aortic strips; efflux responses were increased in low calcium medium and fully antagonized by 3$mM glyburide. Thus, BMS-180448 activates a potassium conductance in both cardiac and smooth muscle. The glyburide sensitivity of the BMS-180448-induced increase in %86&Rb efflux from the aortic preparations suggests that this drug activates I&KATP% in vascular smooth muscle. Moreover, the observation that BMS-180448 (100 $mM) partially inhibits the effects of cromakalim in ventricular muscle cells suggests that these drugs interact, directly or indirectly, with a common site in cardiac muscle.

L6 ANSWER 5 OF 442 BABS COPYRIGHT 2004 BEILSTEIN MDL on STN
AN 6132185 BABS
TI Cardiac Electrophysiologic Effects of **Alinidine**, a Specific

Bradycardic Agent, in the Conscious Dog: Plasma Concentration-Response Relations
AU Boucher, Michel; Chassaing, Claude; Chapuy, Eric
SO J.Cardiovas.Pharmacol. (1995), 25(2), 229 - 233
CODEN: JCPCDT
DT Journal
LA English
SL English
AN 6132185 BABS
AB We studied the cardiac electrophysiologic effects of **alinidine** in conscious dogs. Sinus rate, corrected sinus recovery time (CSRT), and Wenckebach point (WP) were determined in 6 intact dogs. Atrial and ventricular rates, and atrial effective refractory period (AERP) were determined in 6 atrioventricular (AV)-blocked dogs. In both groups, we also measured blood pressure (BP) and plasma **alinidine** concentrations. Each dog received four intravenous (i.v.) injections of 0.5, 0.5, 1, and 2 mg/kg **alinidine** (hydrobromide) 30 min apart. At all doses, **alinidine** decreased sinus rate (<= 43 percent) and ventricular rate (<= 44 percent), but increased atrial rate (<= 31 percent). It lengthened CSRT (<= 71 percent) at the two highest doses and increased AERP (<= 33 percent) and decreased WP (<= 33 percent) at all doses. **Alinidine** did not modify mean BP at any dose in either group. Overall, these results indicate that **alinidine** exhibits electrophysiologic effects in conscious dogs that reflect antiarrythmic potentials of this drug apart from its assumed antiischemic properties.

L6 ANSWER 6 OF 442 BABS COPYRIGHT 2004 BEILSTEIN MDL on STN
AN 5835433 BABS
TI New Cardiovascularly Effective 2-Aryl-2-imidazolinyl-acetic acids/ Syntheses and pharmacological effects
AU Beyerle, R.; Bohn, H.; Schoenafinger, K.; Martorana, P. A.; Bender, H.
SO Arzneim.Forsch. (1985), 35(1), 93-102
CODEN: ARZNAD
DT Journal
LA German
SL English
AN 5835433 BABS
AB The syntheses of new 2-aryl-2-imidazolinyl-acetic acids and esters are reported together with pharmacological results concerning structure-activity relationship.In contrast to the already known but inactive N(1)-alkylated derivatives of 2-arylamino-2-imidazolines the new compounds with an aryl acetic acid substitution in N(1) position of the imidazoline nucleus show the bradykardic activity of the exocyclic alkylated clonidine derivatives such as **alinidine.**The majority of these new substances reduce blood pressure and heart rate in anesthetized rats significantly with a long duration of action. 2-<2-(2.6-Dichloro-phenylamino)-2-imidazoline-1-yl>-2-(2-thienyl)-acetic acid 8a is the most potent compound.Blood pressure is lowered by 30-40 mmHg and heart rate by 175 beats/min with a duration of action > 60 min.The effect is weakened if the thienyl radical is replaced by other heterocycles or if the 2,6-dichlorphenyl group is replaced by a hydrogen atom.The variation of the substituents in the phenyl nucleus shows that the 2,6-dichlorphenyl structure is the optimum substitution pattern, as in the case of clonidine.In the series comprising the 2-<2-(2,6-dichlorphenylamino)-2-imidazoline-1-yl>-2-phenyl acetic acids (8j-8n) the incorporation of different substituents into the phenyl nucleus in the 2-position results in derivatives of different activity.The esters 9a-9c show a faster onset of action as compared to the corresponding carboxylic acid 8a.The most interesting effect of compound 8a in normotensive conscious dogs is a strong and long-lasting decrease in heart rate accompanied by a moderate LVP dp/dt&max% decrease, weak lowering of blood pressure and slight increase in LVEDP.After blocking $b-receptors by atenolol the compound 8a still reduces heart rate.Results in ganglion-blocked and pithed rats indicate a presynaptic and postsynaptic $a&2%-agonistic effect.A decrease insympathetic tone as well as increase

in vagal activity in conscious dogs are considered as possible causes for bradycardic activity.Unlike **alinidine**, however, compound 8a does not affect directly sinus node function.The bradycardic effect of compound 8a which results in a decrease in oxygen consumption is supposed to be the cause of the reduction of infarct size in anesthetized dogs by 28percent.

L6 ANSWER 7 OF 442 BABS COPYRIGHT 2004 BEILSTEIN MDL on STN
AN 5582449 BABS
TI Antihypertensive and Haemodynamic Properties of the Potassium Channel Activating (-)Enantiomer of Cromakalim in Animal Models
AU Clapham, J. C.; Hamilton, T. C.; Longman, S. D.; Buckingham; R. E.; Campbell, C. A.; et al.
SO Arzneim.Forsch. (1991), 41(4), 385-391
CODEN: ARZNAD
DT Journal
LA English
SL English
AN 5582449 BABS
AB The present studies describe the blood pressure lowering, and some other haemodynamic effects, of the potassium channel activator, BRL 38227 ((-) enantiomer of cromakalim, CAS 94470-67-4) in various animal models.BRL 38227 was a potent antihypertensive agent following oral administration to conscious spontaneously hypertensive rats, SHR, (0.038, 0.075 and 0.15 mg/kg), renal hypertensive cats (0.035 and 0.05 mg/kg) and renal hypertensive dogs (0.05 and 0.1 mg/kg).The (+) enantiomer of cromakalim (BRL 38226) was without efect on blood pressure in the conscious rat and cat confirming the stereospecific mode of action of this potassium channel activator.Tachycardia accompanied the antihypertensive effect of BRL 38227 in these models and in the rat this effect could be abolished by pretreatment with atenolol (conscious SHR), diltiazem, verapamil, propanolol and **alinidine** (anaesthetised rats).In addition to reflex tachycardia BRL 38227 also increased plasma renin activity and aldosterone levels in the conscious renal hypertensive cat.In both the anaesthetised normotensive cat (0.001 mg/kg/min i.v.) and dog (0.0025 to 0.02 mg/kg i.v.) BRL 38227 lowered blood pressure and total peripheral resistance while increasing cardiac output via increased heart rate and stroke volume in the cat and via increased heart rate alone in the dog.BRL 38227 reduced renal vascular resistance in both conscious (0.01, 0.015 and 0.02 mg/kg p.o.) and anaesthetised (0.001 mg/kg/min i.v.) cats and the effect was maintained despite marked reductions in blood pressure.In the anaesthetised dog, BRL 38227 was apotent coronary arterial dilator and this effect was also maintained in the face of marked blood pressure lowering activity.The blood pressure lowering activity of BRL 38227 (0.05 mg/kg i.v.), but not that of the calcium slow channel blocker nifedipine (0.1 mg/kg i.v.), was prevented and an established response reversed, by the sulphonylurea drug, glibenclamide (20 mg/kg i.v.), confirming potassium channel activation in vivo.Thus, in animal models BRL 38227 is a potent antihypertensive agent with potentially beneficial effects on renal and coronary perfusion.These effects of BRL 38227 are attributable to activation of glibenclamide-sensitive potassium channels in blood vessels.

L6 ANSWER 8 OF 442 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:303538 CAPLUS
TI β-Cell toxicity of ATP-sensitive K+ channel-blocking insulin secretagogues
AU Rustenbeck, Ingo; Krautheim, Andrea; Jorns, Anne; Steinfelder, Hans Jurgen
CS Institute of Pharmacology and Toxicology, Technical University of Braunschweig, Braunschweig, D-38106, Germany
SO Biochemical Pharmacology (2004), 67(9), 1733-1741
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science B.V.
DT Journal
LA English
AB A prolonged exposure of isolated pancreatic islets to insulin secretagogues, the imidazolines phentolamine, **alinidine** and

idazoxan (100 μM each), the sulfonylurea tolbutamide (500 μM), or the alkaloid quinine (100 μM) resulted in morphol. damage of 4-18% of β-cells compared to less than 2% in controls. Thus, the question arose whether KATP channel-blocking insulin secretagogues are β-cell toxic as has already been suggested for sulfonylureas. The concentration- and time-dependency of the secretagogue-associated toxicity was documented by viability assays in insulin-secreting HIT T15 cells. Treatment for 24 h with idazoxan reduced MTT conversion by 50% at 100 μM and by 98% at 1000 μM. Phentolamine and quinine reduced viability comparably at 1000 μM, but were less toxic at 100 μM. On the other hand, the imidazoline **alinidine** and the sulfonylurea tolbutamide were only moderately toxic (less than 40% viability loss at 1000 μM). The imidazoline efaroxan appeared even to be non-toxic. Apoptotic DNA fragmentation and DEVD-caspase activation was observed at 100 μM of idazoxan and phentolamine, whereas at 1000 μM signs of necrosis predominated. **Alinidine**, tolbutamide and quinine treatment did not increase markers of apoptotic cell death. Blocking Ca2+ influx by D600 did not diminish secretagogue-associated toxicity. Electron microscopy confirmed the validity of these observations for β-cells in intact mouse islets. In summary, β-cell toxicity of the tested insulin secretagogues varied widely and did not depend on a prolonged Ca2+ influx via L-type Ca2+ channels. Thus, secretagogue-mediated closure of KATP channels is apparently not per se β-cell toxic.

L6 ANSWER 9 OF 442 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:254062 CAPLUS
TI Specificity of nonadrenergic imidazoline binding sites in insulin-secreting cells and relation to the block of ATP-sensitive K+ channels
AU Grosse-Lackmann, Timm; Zuenkler, Bernd J.; Rustenbeck, Ingo
CS Institute of Pharmacology and Toxicology, Technical University of Braunschweig, Braunschweig, D-30106, Germany
SO Annals of the New York Academy of Sciences (2003), 1009(Agmatine and Imidazolines), 371-377
CODEN: ANYAA9; ISSN: 0077-8923
PB New York Academy of Sciences
DT Journal
LA English
AB To characterize the specificity of nonadrenergic imidazoline binding sites of insulin-secreting HIT cells, competitive binding of insulinotropic imidazolines and quinine was measured and compared with the effect of these compds. on native KATP channels and with a heterologously expressed variant of the pore-forming subunit (Kir6.2 ΔC26). There were two nonadrenergic imidazoline binding sites for [3H]clonidine with Kd values of 61 nM and 4.5 μM, resp. Quinine reduced specific binding incompletely (73%) with Ki values of 75 nM and 133 μM. Clonidine, N-allyl-clonidine (**alinidine**), and quinine inhibited native KATP channels as well as Kir6.2ΔC26 channels. Coexpression of Kir6.2ΔC26 and SUR1 (the regulatory subunit of KATP) did not increase the potency of quinine. There are nonadrenergic imidazoline binding sites in insulin-secreting HIT cells which also recognize quinine. One of these sites is Kir6.2, the pore-forming subunit of the KATP channel.
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 442 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:964194 CAPLUS
DN 138:33355
TI Treating nerve pain by targeting hyperpolarization-activated, cyclic nucleotide-gated channels (HCN)
IN Chaplan, Sandra; Dubin, Adrienne; Lee, Doo Hyun; Liu, Changlu
PA Ortho-McNeil Pharmaceutical, Inc., USA; The Regents of the University of California
SO PCT Int. Appl., 133 pp.

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002100408	A2	20021219	WO 2002-US16910	20020530
	WO 2002100408	A3	20030731		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	US 2003022812	A1	20030130	US 2002-158684	20020530
	US 2003022813	A1	20030130	US 2002-158711	20020530
	EP 1399162	A2	20040324	EP 2002-734581	20020530

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI	US 2001-297108P	P	20010608
	US 2001-347945P	P	20011107
	US 2002-373012P	P	20020416
	WO 2002-US16910	W	20020530

AB Markedly enhanced activity of pacemaker (hyperpolarization-activated, cation-nonselective, HCN) ion channels governs spontaneous firing in sensory cells of allodynic rats. An HCN ion channel specific blocker, ZD7288, dose-dependently and completely suppresses allodynia. Nerve injury increases the population of large DRG neurons expressing a high d. of Ih and modulates HCN mRNA expression. New methods of treating pain by targeting HCN pacemaker channels are developed. In addition, new methods for identifying compns. useful for treating pain are disclosed.

L6 ANSWER 11 OF 442 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:964124 CAPLUS
DN 138:33351
TI Treating nerve pain by targeting hyperpolarization-activated, cyclic nucleotide-gated channels (HCN)
IN Chaplan, Sandra; Dubin, Adrienne; Guo, Hong-Qing; Lee, Doo Hyun; Liu, Changlu; Luo, Lin; Brown, Sean
PA Ortho-McNeil Pharmaceutical, Inc., USA
SO PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002100328	A2	20021219	WO 2002-US17553	20020530
	WO 2002100328	A3	20030530		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	US 2003022812	A1	20030130	US 2002-158684	20020530
	US 2003022813	A1	20030130	US 2002-158711	20020530
	EP 1402066	A2	20040331	EP 2002-734661	20020530

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

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             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRAI US 2001-297108P   P    20010608
     US 2001-347945P   P    20011107
     US 2002-373012P   P    20020416
     WO 2002-US17553   W    20020530
AB   Markedly enhanced activity of pacemaker (hyperpolarization-activated,
     cation-nonselective, HCN) ion channels governs spontaneous firing in
     sensory cells of allodynic rats.  An HCN ion channel specific blocker,
     ZD7288, dose-dependently and completely suppresses allodynia.  Nerve
     injury increases the population of large DRG neurons expressing a high d.
     of Ih and modulates HCN mRNA expression.  New methods of treating pain by
     targeting HCN pacemaker channels are developed.  In addition, new methods for
     identifying compns. useful for treating pain are disclosed.


=> dis hist

     (FILE 'HOME' ENTERED AT 08:32:07 ON 28 APR 2004)

     FILE 'REGISTRY' ENTERED AT 08:32:20 ON 28 APR 2004
L1             STRUCTURE UPLOADED
L2           0 S L1
L3           0 S L1 SSS FULL

     FILE 'APOLLIT, BABS, CAPLUS, CBNB, CEN, CIN, DISSABS, EMA, IFIPAT,
     JICST-EPLUS, PASCAL, PLASNEWS, PROMT, RAPRA, SCISEARCH, TEXTILETECH,
     USPATFULL, USPAT2, WPIFV, WPINDEX, WTEXTILES' ENTERED AT 08:33:38 ON 28
     APR 2004
L4            18 S CILOBRADINE
L5            13 S L4 AND HYPERTROP?
L6           442 S ALINIDINE
L7            11 S L6 AND HYPERTROP?

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---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                  ENTRY    SESSION
FULL ESTIMATED COST                              103.19     259.24

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                  ENTRY    SESSION
CA SUBSCRIBER PRICE                               -3.47      -3.47

STN INTERNATIONAL LOGOFF AT 08:39:22 ON 28 APR 2004


Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

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